Dual-energy CT tissue segmentation methods for Monte Carlo dose calculations in proton therapy

Valorization

Background

Cancer is a leading cause of death worldwide. The causes, characteristics, risk factors and occurrence of cancer can vary greatly, requiring a constant development of new therapies. Radiotherapy is one of the main treatments for cancer, in which different technologies and types of radiation can be used, such as proton therapy.

In the last decennia, the number of proton therapy centers treating and under construction has increased exponentially, as a measure to provide more precise treatment modality for malign tumours. The characteristic dose distribution of a proton beam in the human body has the potential to decrease short and long term secondary effects of radiation. However, there is a lack of evidence supporting this theoretical advantage of proton therapy, only a few comparison studies indicate its superior outcome compared to x-ray radiotherapy (partially summarized in **Chapter 1**), mostly for children. A new patient selection system that can help bring light to this topic is the dutch model based approach: for each patient with a proton indication, photon (x-ray) and proton treatment plans are calculated and compared, and based on the radiation toxicity levels to the main organs-at-risk (OARs), a choice is made between both radiotherapy modalities. This model might have an important role in providing quantitative evidence of proton therapy's ability to better spare the OARs near a tumour.

Computed tomography (CT) imaging plays a crucial role in radiotherapy treatments, since the treatment plan is made based on the tissue compositions and densities extracted from the processing of each patient CT image. Nevertheless, there is an uncertainty associated with the different CT imaging, scanners and post-processing methods, which are specially relevant for proton therapy, when compared to conventional x-ray radiotherapy, because proton beams deposit most of their energy at the end of a track. To account for such uncertainties, margins are added to the tumour volume to assure that the whole malign mass is irradiated with the necessary dose, however this measure has the cost of increasing the dose to the surrounding healthy tissues.

Monte Carlo (MC) methods are considered the gold-standard for simulations of particle transport and interactions with matter, due to its complex implementation of physical models and libraries. In radiotherapy, MC techniques are needed to better predict the dose distribution in a patient, using directly or indirectly the information extracted from a CT image. While analytical methods may overlook small differences caused by tissues' miss-assignment of atomic composition and density, using MC methods these effects will be taken into account and contribute for the final dose. Besides, MC techniques are used to obtain the linear-energy-transfer (LET) distribution of different particle beams, and can also deal with moving geometries and help to understand inter-play effects between a

moving beam and a moving target. MC's biggest down-side is the computational time needed for accurate simulations, which is highly dependent on the geometry complexity and size, and the number of particles simulated. Nevertheless recent developments in the computer industry have made it possible for vendors of treatment planning systems (TPSs) to start implementing (fast) MC models.

Products and innovation

In this thesis, methodologies of improving accuracy in proton therapy have been studied.

Dual-energy CT dose calculations: We were the first group to develop a platform where dual-energy computed tomography (DECT) images could be used from end-to-end to perform MC dose calculations, a method still not implemented in any commercially available TPS. With this platform, differences in the range of protons using standard images and this new up-rising technology were investigated for phantoms, in which ground truth is known, and on a patient case. For the latter, clinical relevant differences were observed.

Moreover, different DECT modalities and methods were studied through-out this thesis, aiming to investigate the impact of DECT imaging on proton range and dose calculations, and to provide recommendations between DECT systems.

Full implementation of DECT in a TPS is not trivial if the vendor decides to use both DECT images as input. For this, DECT-specific calibrations are needed and the vendor needs to choose one from the different methods published in the last decade, for which validation has been performed in phantom studies using tissue mimicking inserts and animal tissues. An alternative is to calculate a weighted sum of both DECT images (called pseudo-monoenergetic image, PMI), or using CT scanners' own software to convert the DECT images into mass-densities or relative electron densities, that can also be given as input for the TPS.

The wide choice of possibilities dealing with DECT images makes it more difficult for DECT to be implemented on clinical practice, since numerous software and methods are available, and for a TPS vendor to choose one and implement it.

Proton system with a multi-leaf collimator: We were also the first group to model a proton therapy system with an unique multi-leaf collimator at the end of the beam line (the Adaptive Aperture™, a product of Mevion Medical Systems, Inc., Littelton, USA) used to improved the sharpness of proton beams, hence decreasing the dose given laterally to healthy tissues and OARs. The development of the beam model was done parallel to the clinical implementation of this component and in close collaboration with the manufacturer, enabling the study of several features from this device and even investigate how to improve it. This model aims also to be used as an independent MC dose calculation platform with respect to the available TPS.

Furthermore, we also proved the feasibility of using this multi-leaf collimator combined with a precise imaging platform for irradiation of small-animals, a complete different field for which the system was not intended, greatly expanding its research capabilities. Pre-

clinical research is a corner stone of scientific developments in radiotherapy, from which new methodologies can be translated to clinical practice. Proton therapy is no exception and there is a need for pre-clinical experiments, however the cost of building a dedicated system is too high for most research facilities, making the option of adapting an existing clinical system very attractive. In this field, pre-clinical studies can help understand the biological impact of proton beams compared to standard radiotherapy, the impact on cell damage when using proton beam at different dose rates, or to investigate the potential benefit of combining proton therapy with immunotherapy, dose enhancers and other drugs.

Challenges and future perspectives

The translation of proton therapy from physics institutes and laboratories to clinical practice has brought numerous topics of research for the scientific community. The main goal is to assure the quality of treatment, in which the entire tumour is irradiated with the necessary dose to treat the patient, and at the same time the minimum amount of healthy tissue is irradiated with high doses.

On the other hand, particle therapy centers are considered the single most expensive specialized medical tool for cancer treatment, where treatment cost greatly exceeds the one from conventional radiotherapy. For this reason, a concern has been raised that proton therapy will be overused for common cancer for which evidence for proton therapy is still unclear, due to the potential profit it may bring for the medical institution. To decrease the cost of a proton therapy center, more compact single-room facilities have appear on the market in the last years, making its construction more affordable worldwide.

With respect to the topics investigated in this thesis, DECT potential improvement over single-energy CT might not be good enough to achieve the level of uncertainty desired in tissue segmentation and proton range prediction. Hence, other technologies have appeared as potential better alternatives, such as triple-energy CT or spectral CT. Another alternative might be the use of proton beams for imaging, called *proton CT*, which provides a direct measurement of tissue's proton stopping powers. For either case, there is a need to verify the method used by means of *in vivo* measurements of proton range, without which final validation of the methods is not achievable. These methods discussed in **Chapter 7**, are still under-development and not yet at a level of becoming part of clinical practice.

Furthermore, during the course of a treatment that can take up to seven weeks, the patient's anatomy can change drastically while the tumour can shrink/expand or move to a different location. It is for this reason necessary to do treatment adaption with the help of weekly or daily imaging. Currently, centers that do treatment adaptation, do it by recalculating the plan after seeing relevant differences on interfractions CT. However, intrafaction motion or irregularities are not measured. A future goal for treatment adaptation would be to do it online, in which the patient is positioned, the plan is partially delivered and with *in vivo* measurements the dose is verified and the plan adapted *in loco* if needed.

Target groups and social impact

The patient is the first to benefit from a more accurate proton therapy treatment. The use of large margins added around the tumour to assure full coverage and to account for all

uncertainty sources can be decreased by improving the accuracy of tissue segmentation and mass-density conversion, and by using with proper *in vivo* verification methods. Large margins imply that healthy tissue will be irradiated with a high dose, which can lead to short and long term side effects, including the growth of secondary tumours, that can have an considerable impact on the patient's quality of life and life expectancy. For this reason, proton therapy could be ideal for treating children and young adults. Many questions about the potential of proton therapy are still unanswered, for which there is an urgent need to perform clinical (and pre-clinical) trials and follow closely the patients treated with different radiotherapy modalities for many decades.